NOD2 gene

nucleotide binding oligomerization domain containing 2

Normal Function

The *NOD2* gene provides instructions for making a protein that plays an important role in immune system function. The NOD2 protein is active in some types of immune system cells (including monocytes, macrophages, and dendritic cells), which help protect the body against foreign invaders such as viruses and bacteria. The protein is also active in several types of epithelial cells, including Paneth cells, which are found in the lining of the intestine. These cells help defend the intestinal wall against bacterial infection.

The NOD2 protein has several critical functions in defending the body against foreign invaders. The protein is involved in recognizing certain bacteria and stimulating the immune system to respond properly. When triggered by specific substances produced by bacteria, the NOD2 protein turns on (activates) a protein complex called nuclear factor-kappa-B. This protein complex regulates the activity of multiple genes, including genes that control immune responses and inflammatory reactions. An inflammatory reaction occurs when the immune system sends signaling molecules and white blood cells to a site of injury or disease to fight microbial invaders and facilitate tissue repair.

The NOD2 protein also appears to play a role in a process called autophagy, which cells use to surround and destroy bacteria and viruses. In addition to protecting cells from infection, autophagy is used to recycle worn-out cell parts and break down certain proteins when they are no longer needed. This process is also involved in the self-destruction of cells (apoptosis).

Health Conditions Related to Genetic Changes

Blau syndrome

At least 17 mutations in the *NOD2* gene have been found to cause Blau syndrome, an inflammatory disorder that primarily affects the skin, joints, and eyes. These mutations change single protein building blocks (amino acids) in the NOD2 protein. All of these mutations result in a version of the NOD2 protein that is overactive, which can trigger an abnormal inflammatory reaction and cause swelling and irritation. However, it is unclear how the abnormally active protein causes the specific pattern of inflammation affecting the skin, joints, and eyes that is characteristic of Blau syndrome.

NOD2 gene mutations can also cause early-onset sarcoidosis, a similar condition that some researchers consider to be a non-inherited version of Blau syndrome.

Crohn disease

Approximately 40 variations in the *NOD2* gene have been associated with an increased risk of Crohn disease, a complex disorder of the digestive system. In particular, *NOD2* gene changes are associated with a form of Crohn disease that affects the lower part of the small intestine (the ileum) in populations of northern European descent. The most common variation, written as 3020insC or 1007fs, leads to the production of a NOD2 protein that is slightly shorter than normal. Other common variations change single amino acids in the NOD2 protein. It is unclear how these genetic changes increase the risk of developing Crohn disease. Studies suggest that changes in the *NOD2* gene prevent the protein from recognizing bacteria, allowing these microbes to grow unchecked and invade cells that line the intestine. An abnormal immune response to these bacteria may contribute to chronic inflammation and the digestive problems characteristic of Crohn disease.

cancers

A few studies have suggested a possible association between changes in the *NOD2* gene, particularly the common variation 3020insC, and the development of several types of cancer. Although some of these studies found an increased risk of cancer in people with a *NOD2* gene variation, other research found no such association. It is unclear how changes in this gene might contribute to cancer risk.

other disorders

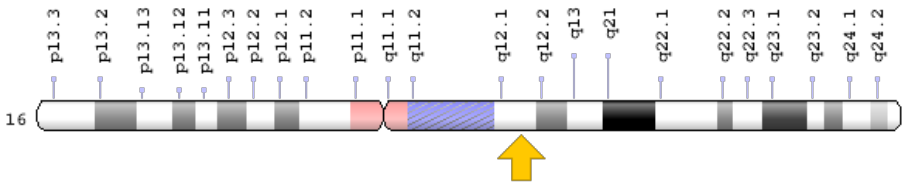
Several studies have considered variations in the *NOD2* gene as a possible risk factor for a condition called graft-versus-host disease (GVHD). Graft-versus-host disease can occur following certain cancer treatments, such as allogeneic stem cell transplantation. This procedure, which is typically used to treat cancers of the blood and immune system, replaces a patient's diseased blood-forming cells (a type of stem cell) with stem cells from a healthy donor. If the donor's stem cells (the graft) recognize the patient's body (the host) as foreign, they may attack organs and tissues such as the liver, digestive system, and skin. Graft-versus-host disease is the term used to describe this potentially severe reaction.

A few studies have suggested that variations in the *NOD2* gene influence the risk of developing severe complications of graft-versus-host disease following an allogeneic stem cell transplant. The presence of *NOD2* gene variations in both the stem cell donor and the recipient is associated with the greatest risk of a severe reaction. However, other research has found no relationship between *NOD2* gene changes and the risk of developing graft-versus-host disease.

Chromosomal Location

Cytogenetic Location: 16q12.1, which is the long (q) arm of chromosome 16 at position 12.1

Molecular Location: base pairs 50,693,581 to 50,733,077 on chromosome 16 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ACUG
- BLAU
- CARD15
- caspase recruitment domain family, member 15
- caspase recruitment domain protein 15
- CD
- IBD1
- inflammatory bowel disease protein 1
- LRR-containing protein
- NOD2_HUMAN
- NOD2B
- nucleotide-binding oligomerization domain containing 2
- PSORAS1

Additional Information & Resources

Educational Resources

- Immunobiology: The Immune System in Health and Disease (fifth edition, 2001): The Front Line of Host Defense
  https://www.ncbi.nlm.nih.gov/books/NBK27105/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28CARD15%5BTIAB%5D%29+OR+%28NOD2%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN PROTEIN 2
  http://omim.org/entry/605956

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_NOD2.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=NOD2%5Bgene%5D
- HGNC Gene Family: Caspase recruitment domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/959
- HGNC Gene Family: NLR family
  http://www.genenames.org/cgi-bin/genefamilies/set/666
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=5331
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/64127
- UniProt
  http://www.uniprot.org/uniprot/Q9HC29

Sources for This Summary

- Borzutzky A, Fried A, Chou J, Bonilla FA, Kim S, Dedeoglu F. NOD2-associated diseases: Bridging innate immunity and autoinflammation. Clin Immunol. 2010 Mar;134(3):251-61. doi: 10.1016/j.clim.2009.05.005. Epub 2009 May 24. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19467619
- Elmaagacli AH, Koldehoff M, Hindahl H, Steckel NK, Trenschel R, Peceny R, Ottinger H, Rath PM, Ross RS, Roggendorf M, Grosse-Wilde H, Beelen DW. Mutations in innate immune system NOD2/CARD 15 and TLR-4 (Thr399Ile) genes influence the risk for severe acute graft-versus-host disease in patients who underwent an allogeneic transplantation. Transplantation. 2006 Jan 27; 81(2):247-54.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16436969

- Gasche C, Grundtner P. Genotypes and phenotypes in Crohn's disease: do they help in clinical management? Gut. 2005 Jan;54(1):162-7. Review. Erratum in: Gut. 2005 Mar;54(3):442.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15591523
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1774386/
- Gaya DR, Russell RK, Nimmo ER, Satsangi J. New genes in inflammatory bowel disease: lessons for complex diseases? Lancet. 2006 Apr 15;367(9518):1271-84. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16631883
- Henckaerts L, Vermeire S. NOD2/CARD15 disease associations other than Crohn's disease. Inflamm Bowel Dis. 2007 Feb;13(2):235-41. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17206682
- Holler E, Rogler G, Herfarth H, Brenmoehl J, Wild PJ, Hahn J, Eissner G, Schölmerich J, Andreesen R. Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GvHD following allogeneic stem cell transplantation. Blood. 2004 Aug 1;104(3): 889-94. Epub 2004 Apr 15.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15090455
- Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001 May 31;411(6837):599-603.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11385576
- Hugot JP. CARD15/NOD2 mutations in Crohn's disease. Ann N Y Acad Sci. 2006 Aug;1072:9-18. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17057186
- Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, Fuji A, Yuasa T, Manki A, Sakurai Y, Nakajima M, Kobayashi H, Fujiwara I, Tsutsumi H, Utani A, Nishigori C, Heike T, Nakahata T, Miyachi Y. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. Blood. 2005 Feb 1;105(3): 1195-7. Epub 2004 Sep 30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15459013
- Kutikhin AG. Role of NOD1/CARD4 and NOD2/CARD15 gene polymorphisms in cancer etiology. Hum Immunol. 2011 Oct;72(10):955-68. doi: 10.1016/j.humimm.2011.06.003. Epub 2011 Jul 13. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21745515
- Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Häfner R, Chamaillard M, Zouali H, Thomas G, Hugot JP. CARD15 mutations in Blau syndrome. Nat Genet. 2001 Sep;29(1): 19-20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11528384
- Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001 May 31;411(6837):603-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11385577
- Rogler G, Holler E. Can NOD2/CARD15 mutations predict intestinal graft-versus-host disease and aid our understanding of Crohn's disease? Nat Clin Pract Gastroenterol Hepatol. 2004 Dec;1(2): 62-3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16265048

- Strober W, Kitani A, Fuss I, Asano N, Watanabe T. The molecular basis of NOD2 susceptibility mutations in Crohn's disease. Mucosal Immunol. 2008 Nov;1 Suppl 1:S5-9. doi: 10.1038/mi.2008.42. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19079230
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665012/
- Strober W, Watanabe T. NOD2, an intracellular innate immune sensor involved in host defense and Crohn's disease. Mucosal Immunol. 2011 Sep;4(5):484-95. doi: 10.1038/mi.2011.29. Epub 2011 Jul 13. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21750585
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3773501/
- Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, Inohara N, Nunez G, Tromp G, Williams CJ. CARD15 mutations in familial granulomatosis syndromes: a study of the original Blau syndrome kindred and other families with large-vessel arteritis and cranial neuropathy. Arthritis Rheum. 2002 Nov;46(11):3041-5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12428248

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/NOD2

Reviewed: July 2012
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services